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# Ring Strain in [*n*]ladderanes

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The ring strain energies in a series of [*n*]ladderanes ($n = 3-8$) have been calculated by using high-level ab initio method (G3MP2//B3LYP-6−31G*) and the series of isodesmic, homodesmotic, and protobranching compensated reactions. The results show that various four-member rings incorporated into the ladderane chain have different strain energies and that the total strain in a ladderane molecule is smaller than the corresponding sum of strain energies of the cyclobutane rings.

## Introduction

The strain in organic molecules which contain three- or four-member rings has been studied extensively because such compounds present challenges for the existing synthetic methodologies and may also furnish new substances with novel, useful properties. An example of such class of molecules are [*n*]ladderanes.[1] These molecules were expected to be highly strained (due to the accumulation of fused, strained, 4-member rings) and thus not common in nature. Yet the substituted [3] and [5]ladderanes were found in the cell membranes of anaerobic ammonium oxidizing bacteria. Ladderanes are difficult to prepare using conventional methods of organic synthesis but can be obtained in excellent yield using supramolecular approach.[1] The synthesis uses linear polyene derivatives and hydrogen bonded template. It is carried out in the solvent-free, solid state environment where reactant molecules are preorganized into spatial configuration suitable for the subsequent photoaddition reaction. Surprisingly, only two theoretical studies on ladderanes have been reported.[2,3] These studies were performed by semiempirical or DFT methods rather than by the high level methods. The molecular properties obtained in these studies[3] included enthalpy of formation, HOMO−LUMO energy gap, vibrational frequencies, and proton NMR chemical shifts. Furthermore, Santos and Fuentealba[3] used a less accurate value for cyclobutane enthalpy and performed their calculations only for ladderanes with odd values of [*n*].

We used high level ab initio calculations to investigate the molecular strain in all-trans ladderanes and check the previously reported claims about the expected high strain in these molecules. The molecular size of larger ladderanes makes them less amenable to high level ab initio calculations and this could be the reason for paucity of computational studies. We are also interested in determining whether the individual rings possess different strain energies or not.

## Theoretical Methods

The quantum chemical calculations were performed with the Gaussian 03 program.[4] The total electronic energy for each molecule was computed using the G3MP2/B3LYP method[5] which has root-mean-square deviation of at least 4 kJ/mol. The method includes full geometry optimization at the B3LYP/6−31G* level followed by single point QCISD type calculations. All of the optimized structures corresponded to the minima on their potential energy surfaces as was inferred from the absence of imaginary vibrational frequencies. The selected geometry parameters of optimized geometries for [3] and [5]ladderanes are shown in Scheme 1. The experimental geometries available for ladderanes are those of tetrapyridine substituted [3] and [5]ladderanes, rather than the parent unsubstituted ladderanes. The substitution together with the crystal packing forces may account for the observed differences between the experimental and the calculated geometries.

The unsubstituted ladderanes have not been prepared and their molecular structures not determined experimentally. The calculated structures have higher symmetries than those in the solid state so we have investigated the stability of our wave functions obtained upon geometry optimization and found them to be stable toward geometry distortion or spin state change. Examples of calculated geometries are given in Scheme 1 and Figure 1. In all of the ladderanes, the calculated geometries show that cyclobutane rings are planar and that each molecule has a symmetry plane bisecting all of the rings.

In order to estimate the total and individual ring strain energies (RSE) in ladderanes, we used three different reaction schemes: isodesmic reactions (Supporting Information, Scheme A), homodesmotic reactions[6] (Supporting Information, Scheme B) and the protobranching balanced isodesmic reactions (Schemes 2 and 3). Experimental standard enthalpies of formation of ladderanes have not been reported. However, we tested the reliability of our calculated reaction enthalpies for the reactions in Scheme 2 by comparing the calculated RSE with experimental enthalpies for cyclobutane, ethane, and *n*-hexane[1a,7] using the isodesmic reaction: $C_4H_8 + C_2H_6 = C_6H_{14}$. The "experimentally derived" (using experimental enthalpies in isodesmic reaction) RSE for cyclobutane is 110.04 kJ/mol[1a] while the calculated value using isodesmic reactions and G3MP2B3 method is 111.6 kJ/mol. We have also calculated standard enthalpies of formation for cyclobutane and [2,2,0]bicyclohexane which amount to 30.2 and 132 kJ/mol, respectively. These values compare favorably with experimental values from thermochemical databases[7,8] which amount to 27.6 and 125 kJ/mol, respectively. The satisfactory agreement obtained between calculated and experimental values gives us confidence in the RSE values obtained for ladderanes. We have calculated the standard enthalpies of formation (using atomization method) for the title molecules and summarized them in Table 1. The specific isodesmic and homodesmotic reactions used for calculating total strain energies are given in Supporting Information (Schemes A and B) and

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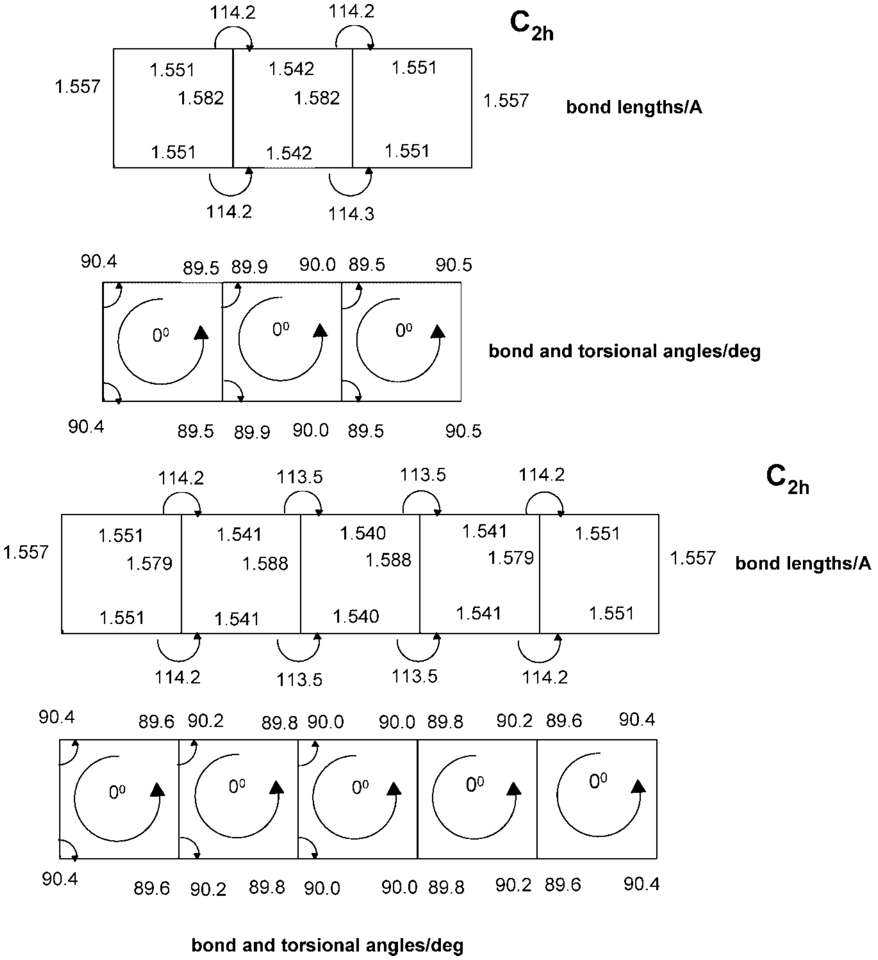
**SCHEME 1: Calculated Geometry Parameters in [3] and [5]ladderanes at B3LYP/6-31G* Level**



the energies obtained from different reaction schemes are compared in Table 2. The protobranching balanced isodesmic reactions are given in Schemes 2 and 3.

When calculating ring strain in small alkanes, it has recently been pointed out that the existence of 1,3-alkyl−alkyl group interactions may lead to considerable errors in estimating strain energies.[9] We have, therefore, in addition to the traditional isodesmic and homodesmotic reaction schemes[6] used the reactions schemes in which the total number of “protobranching” (1,3-alkyl−alkyl) group interactions is the same on both sides of the reaction equation.

## Results and Discussion

It has been stated that ladderanes are highly strained molecules due to the fusion of four member rings.[1] Fusion of such rings leads to significant reduction of the two CCC bond angles at the bridgehead carbons. In cyclobutane, on the other hand, there is only one CCC angle per carbon atom whose magnitude is significantly reduced from the tetrahedral value. This simple argument suggests that ladderanes should have larger total ring strain than the net sum of cyclobutane rings. In order to test this assumption, we have calculated the total strain energies in ladderanes by adding RSE of the constituent cyclobutane rings. The results in Table 2 show that, irrespective

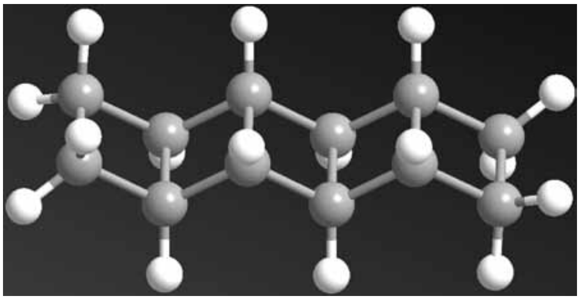
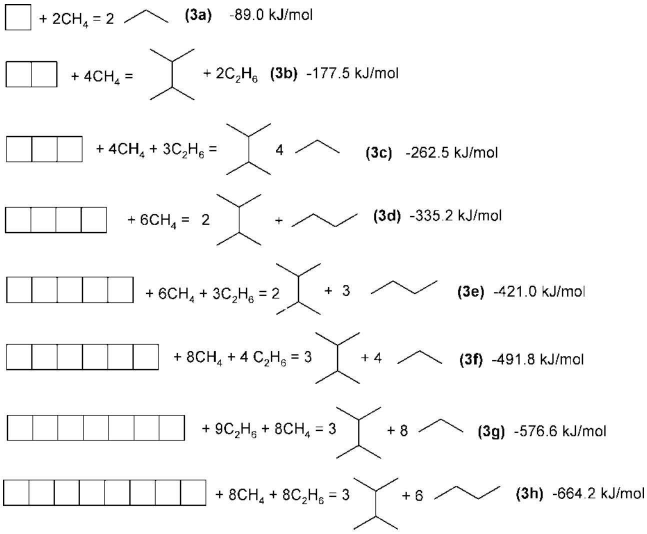


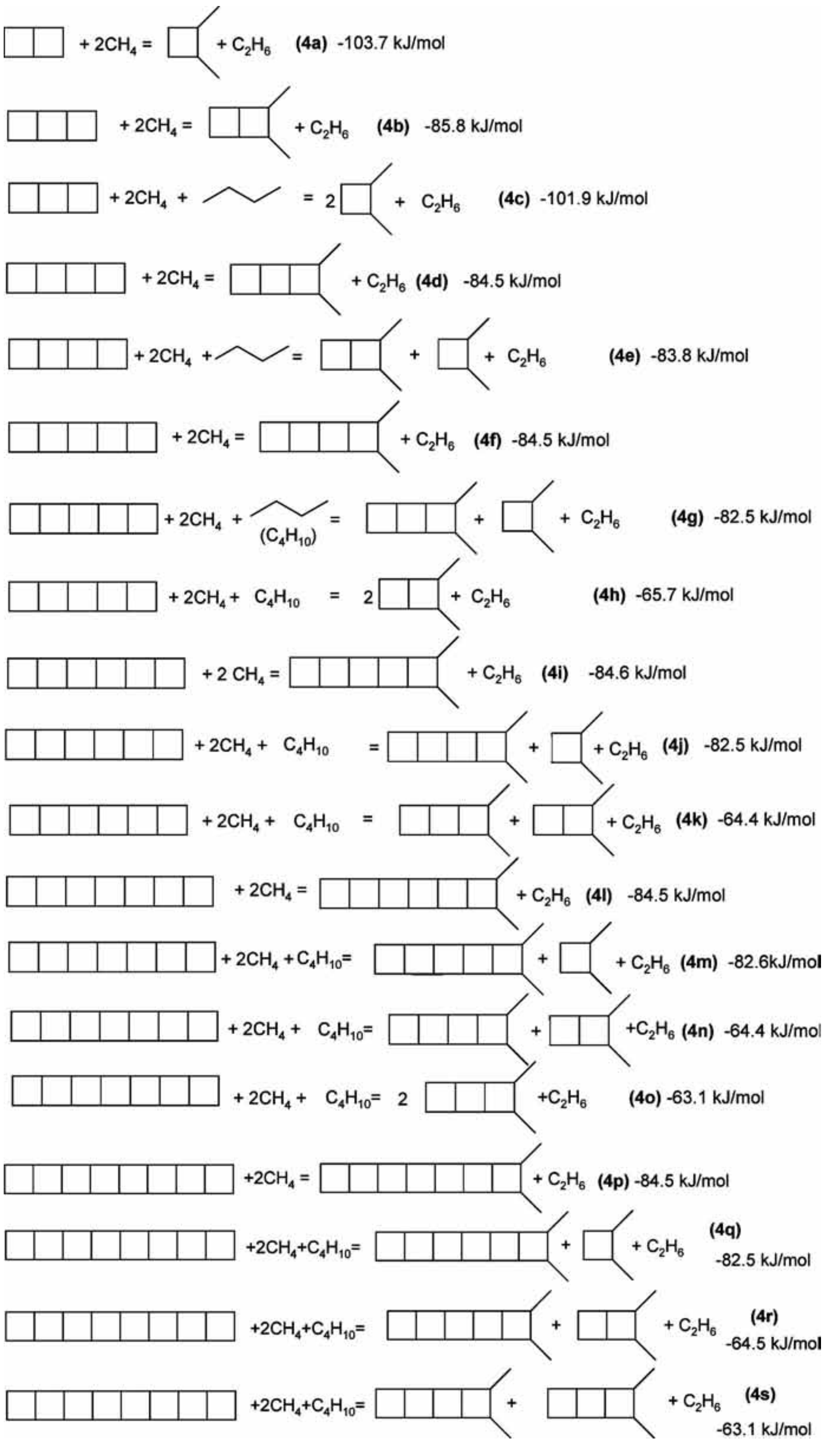
**Figure 1.** Optimized structure of [5]ladderane.

**SCHEME 2**



total strain energies in ladderanes determined by protobranching balanced reactions

**SCHEME 3: Protobranching Balanced Reactions Used to Calculate Individual Ring Strain**



of the reaction scheme employed, the RSE values are not additive and do not increase linearly with the number of fused rings. The total strain is larger than the sum of individual ring strains, especially for larger ladderanes with $n > 3$. This observation suggests that the strain energies of individual rings are not transferable and that the strain in one ring may influence the strain in the neighboring ones. This conclusion raises further possibility that some rings have larger strain than others. We have set up the appropriate reaction schemes and obtained individual ring strain energies (Schemes 3 and 4 and Scheme C in Supporting Information). When the individual ring strain energies are added (Table 2), it appears that the sum is smaller than the total strain in a particular ladderane. This observation is consistent with the notion that part of the individual ring strain is distributed along the chain.

The ring strain decreases on going from the outer to the inner rings (Scheme 4). This conclusion is arrived at by two different reaction schemes which suggests that the change in the

**TABLE 1: Calculated and Experimental Standard Enthalpies of Formation**[a,b]

| molecule | $\Delta H_f^0$ kJ/mol |
|---|---|
| cyclobutane | 30.2 (27.6) |
| [2.2.0]bicyclohexane | 132 (125) |
| [3]ladderane | 217.8 (*224.7*) |
| [4]ladderane | 303.5 |
| [5]ladderane | 389.1 (*413.8*) |
| [6]ladderane | 474.7 |
| [7]ladderane | 560.3 (*602.9*) |
| [8]ladderane | 645.9 |

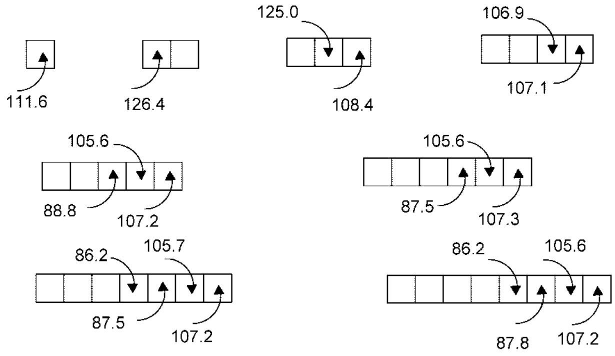
[a] The experimental values are in brackets. [b] The values in italic font are from ref 3.

**TABLE 2: Ring Strain Energies (kJ/mol) Calculated Using Homodesmotic(Homo), Isodesmic (BSE) and Protobranching Compensated (Proto) Reaction Schemes Together with the Sums of Individual Ring Strain Energies (Σ) Calculated Using Homo and Proto Schemes**[a]

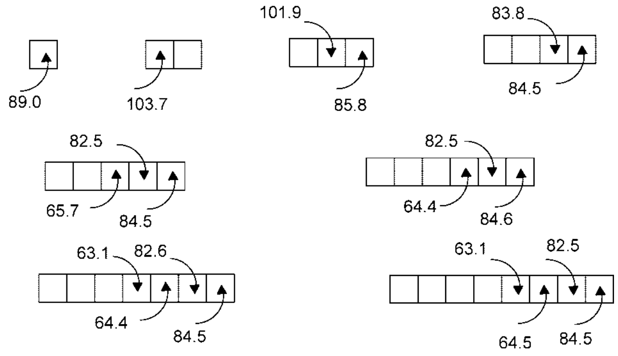
| molecule (symmetry) | BSE | homo | Σ homo | proto | Σ proto |
|---|---|---|---|---|---|
| cyclobutane $C_{2v}$ | 66.4 | 111.6 | | 89.0 | |
| [2.2.0]bicylohexane $C_{2v}$ | 122.1 | 229.9 | 252.8 | 177.6 | 207.4 |
| [3]ladderane $C_{2h}$ | 161.8 | 332.0 | 341.8 | 262.5 | 273.5 |
| [4]ladderane $C_{2v}$ | 202.4 | 434.0 | 428.0 | 335.2 | 336.6 |
| [5]ladderane $C_{2h}$ | 240.8 | 536.0 | 514.4 | 421.0 | 399.7 |
| [6]ladderane $C_{2v}$ | 280.2 | 638.0 | 600.8 | 491.8 | 463.0 |
| [7]ladderane $C_{2h}$ | 319.7 | 739.9 | 687.0 | 576.6 | 526.1 |
| [8]ladderane $C_{2v}$ | 359.2 | 841.9 | 773.6 | 664.2 | 589.2 |

[a] See Scheme 5 for the graphical depiction of strains of individual rings.

**SCHEME 4**



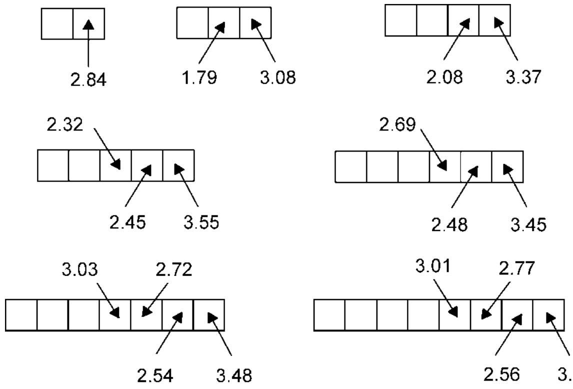
individual ring strain calculated from homodesmotic reactions



individual ring strain calculated from protobranching reactions

constituent ring strain is not an artifact of a particular computational method.

**SCHEME 5: Magnetic Measures of σ-Antiaromaticity**



NICS (0) shifts in ladderanes

Is there any other evidence to support the claim of different strains in individual rings? The calculated geometries (Scheme 1) indicate that CC bonds in the outer rings are shorter than those in the inner ones which is consistent with the larger strain in the former. Furthermore, the calculation of aromaticity of constituent rings provides further indication that rings have different properties. We have calculated the nucleus independent chemical shifts[6] NICS(0) for different rings (Scheme 5). Four member rings are considered σ-antiaromatic which is born out by positive NICS values. Also, the NICS values for different rings differ which suggests that they can not be considered identical. This is consistent with calculated differences in the constituent ring strain energies.

## Summary

We have determined the strain energy in ladderanes on the basis of high-level ab initio calculations. The total strain in ladderanes is smaller than the corresponding multiple of cylobutane strain energies. This discrepancy becomes progressively larger as the ladderane chain gets longer. The only exceptions are cyclobutane and [2,2,0]bicyclohexane. On the other hand, the total strain energy is larger than the sum of strains in individual rings. This suggests that the strain energy is redistributed along the chain. Furthermore, the strain of the two outermost rings is approximately 15 kJ/mol higher than of the inner rings. This nonuniformity in ring strain may have interesting consequences for chemical reactivity of ladderanes which to date remains unexplored. Thus, one can speculate that the most reactive sites in ladderane molecules are the rings at the ends of the molecule. The reaction at the molecular edge may cause ring opening thus turning the inner rings into the molecular edges. This may lead to stepwise molecular decomposition in the "zipper-like" manner, that is, the splitting of the molecule in the manner of opening the zipper.

Currently, we know very little about the reactivity of these interesting molecules and this computational work may provide an incentive for future more detailed studies.

**Supporting Information Available:** G3(MP2)//B3LYP energies, calculated geometries, and reaction schemes for ladderanes. This information is available free of charge via the Internet at http://pubs.acs.org.

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